Resolution of celiac disease, IgA deficiency and platelet refractoriness after allogeneic bone marrow transplantation for acute leukemia

Allogeneic stem cell transplantation is a high-risk procedure which has traditionally been reserved for the treatment of immediately life-threatening hematologic malignancies which have failed less intensive therapies. With advances in supportive care, conditioning regimens, and immune suppression, however, transplant outcomes have markedly improved.[1,2] Consequently, it is increasingly acceptable to apply it to non-malignant disorders such as congenital or inherited immunodeficiency syndromes, hemoglobinopathies[3,4] and autoimmune diseases.[5,6] Stem cell transplantation is the only curative treatment in autoimmune diseases, as the non-malignant B-lymphocytes underlying many of these diseases are often difficult to eradicate with non-myeloablative chemotherapy. Through the myeloablative chemotherapy and stem cell rescue with the additional cell-mediated clearance provided by graft-*versus*-host effect, durable cure may be achieved. The presence of immunopathologies may predispose patients to alloimmunization, which in turn may make supportive care during the transplant period especially challenging. We report a case of a woman with celiac disease who underwent stem cell transplantation for acute leukemia. The presence of concurrent anti-IgA and anti-HLA antibodies greatly complicated the provision of supportive transfusion care, but these immune conditions were ultimately cured by the stem cell transplantation itself.

A 63-year-old female patient presented with secondary acute myeloid leukemia (AML) after an initial diagnosis of chronic myelomonocytic leukemia (CMML-1). Her past medical history was remarkable for celiac disease confirmed by endoscopic biopsy following a two-week dietary gluten challenge (serology for tissue transglutaminase/anti-gliadin antibodies was not performed). She was subsequently found to have the celiac-associated HLA DRB1•0301, DQB1•0201. Following her diagnosis, she was maintained on a gluten-free diet with occasional consumption of gluten-rich food and no recurrence of symptoms. In addition, she had a history of absolute IgA deficiency diagnosed concurrently with her celiac disease, with anti-IgA antibodies confirmed by the ID-PaGIA IgA (DiaMed) assay. Her family history was notable for leukemia in her maternal grandfather, celiac disease in a paternal grandmother, and breast and bone cancer in two maternal aunts. Other family members include two siblings and three children without significant medical conditions.

Within two months of being diagnosed, the patient's CMML-1 transformed into secondary acute myelogenous leukemia characterized by a normal karyotype and positivity for both FLT-3 (ITD) and NPM1 mutations.

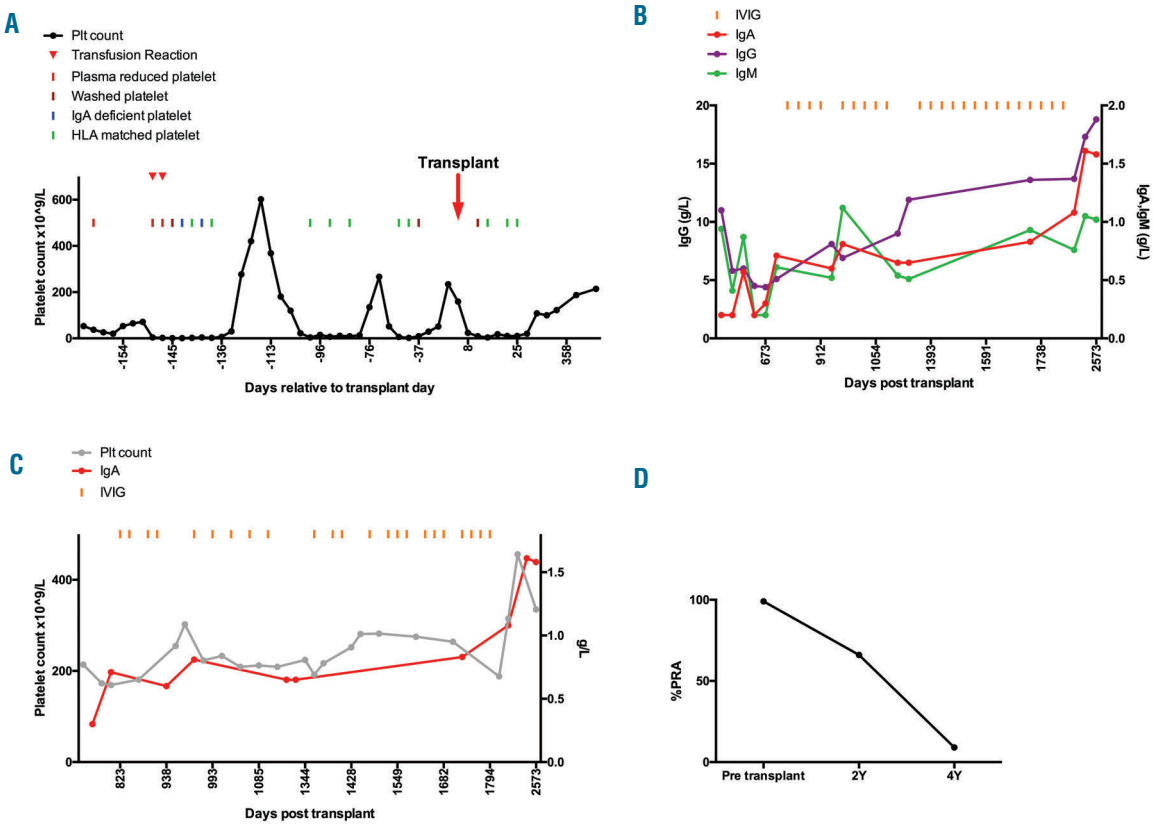

Figure 1. Transfusion support at the time of transplantation complicated by IgA deficiency and platelet refractoriness. (A) History of platelet transfusion, platelet counts and transfusion reaction peri transplantation, all products were irradiated before transfusion. (B) Gradual normalization of Immunoglobulin levels post transplantation and IVIG transfusion history. (C) IgA level and platelet counts normalized post transplantation. (D) Calculated panel reactive antibody (PRA) pre and post transplantation. Plt: platelet.

Induction was initiated with NOVE-HiDAC protocol (mitroxantrone, etoposide, and high-dose cytarabine),[7] followed by two rounds of consolidation with mitoxantrone and cytarabine; treatment was complicated by oral mucositis, which was treated with acyclovir. Following achievement of complete remission, the patient underwent an allogeneic stem cell transplant using the R-FBT (400)-CSMF protocol of fludarabine, busulfan and total body irradiation for myeloablation, with four courses of methotrexate for graft-*versus*-host disease (GvHD) prophylaxis. A sister with a 6/6 HLA match and similar HLA haplotype in DRB1•03, DQB1•0201 regions served as the stem cell donor; both donor and recipient were group A-RhD positive and CMV-seronegative. A stem cell dose of $2.41x10^6$ cells/kg CD34+ cells was administered and during the engraftment period the patient experienced an episode of neutropenic fever with coagulase-negative Staphylococcus, treated with vancomycin. Engraftment was documented on day +29 and she was discharged home three days later in a stable condition.

Throughout this period, provision of platelet transfusion support was complicated by both anaphylactic transfusion reactions (secondary to anti-IgA antibodies) and refractory thrombocytopenia (due to anti-HLA antibodies with a calculated panel reactive antibody [PRA] of nearly 100% by Luminex flow bead assay). Sourcing blood products from IgA-deficient donors, while effective in preventing transfusion reactions, was not a sustainable option for this patient due to very few donors in the country who were HLA compatible. The only option for platelet transfusion was to source HLA-matched platelets and then attempt to remove all residual IgA through washing with 0.9% saline. While such an approach is also known to be effective in preventing transfusion reactions,[8] it proved logistically challenging at our center due to the lack of a product centrifuge within our institution's cancer treatment center, and the relatively short expiry time (4 hours) of platelets after undergoing this type of manipulation. In addition, the degree of washing required to completely remove allergen from platelet products results in significant loss of hemostatic effect.[9] The approach combined partial platelet washing and cautious pre-medication, plus adjunctive use of tranexamic acid to decrease the need for platelet transfusions altogether. She survived several months of aplasia after the stem cell transplant, albeit with recurrent epistaxis severe enough to require surgical intervention, and had several episodes of moderate-severity allergic transfusion reactions. We observed brief episodes of thrombocytosis shortly after the induction and immediately after transplantation; bone marrow studies performed at this time reported a repopulating hematopoietic tissue. Her complete platelet transfusion history is demonstrated in (Figure 1A).

At 30 days post transplant, the patient returned with an episode of elevated liver transaminases at 2-3 times normal accompanied by frequent bowel movements, and was diagnosed with cyclosporine toxicity (serum level 778), although GvHD could not be ruled out. At three months post transplant, however, she experienced a diffuse macular rash and a recurrent elevation in her liver enzymes that was diagnosed as stage III chronic GvHD. GvHD was successfully treated with prednisone 1 mg/kg and cyclosporine that subsequently tapered and substituted with azathioprine. At six months post-transplant, she continued to show signs of liver GvHD and, accordingly, her azathioprine was changed to mycophenylate mofetil. This medication was discontinued at two years post transplant with no signs of recurrent GvHD.

Following her stem cell transplant, the patient's immunoglobulin (Ig) level was initially maintained within normal range through monthly IVIG infusion. During this time, the quantification of the patient's IgA level that preceded her IVIG infusions gradually normalized (Figure1B). Additional testing confirmed that her previously diagnosed anti-IgA antibodies were now undetectable; IgA levels remained within normal range even after her IVIG infusions were discontinued (Figure1C). This prompted a repeat assessment of her previously high degree of anti-HLA sensitization, which had remained high during the first two years post transplant despite the absence of any ongoing platelet transfusion support. Four years after transplant, the CPRA had fallen from 99% to 9% (Figure 1D). On the assumption that both phenomena represented clearance of native plasma cells, the patient's history of celiac disease was also reassessed through measurement of tissue tTG IgG and deamidated Gliadin IgG levels. These, too, were negative, suggesting that the patient's celiac disease had also been cured, although she has nonetheless decided to maintain a gluten-free diet with occasional deviation and remains completely asymptomatic. She is currently approximately seven years post transplant and remains in remission without evidence of GvHD or other long-term complications.

Transfer of IgA deficiency from donor to recipient of alloSCT and correction of IgA deficiency has been reported previously;[10,11] however, to our knowledge, this is the first reported case of simultaneous resolution of IgA deficiency, platelet refractoriness and celiac disease accompanying the cure of a hematologic malignancy. The correction of immune diseases by stem cell transplants, including the resolution of celiac disease, multiple sclerosis and systemic sclerosis has been documented previously.[12,13,14] The absence of symptoms or serology associated with celiac disease in the post-transplant period could have reflected the ongoing avoidance of gluten in the patient's diet. However, it is notable that the patient's donor sibling, despite maintaining a gluten-rich diet, has herself remained free of celiac disease even though she shared the same celiac-associated HLA allele as the patient. The etiology of celiac disease is multifactorial and only 3% of the individuals with the celiac associated HLA develop signs or symptoms of the disease. Given the clearance of other pathological antibodies during the post-transplant period (i.e., anti-HLA and anti-IgA antibodies), we speculate that the patient has similarly been cured of celiac disease. The presumed mechanism was clearance of disease-associated B-cells, via a combination of myeloablative chemotherapy and possible graft-*versus*-host-disease. Moreover, the gradual return of IgA levels to normal in the post-transplant period can be attributed to the replacement of host plasma cells with donor plasma cells capable of IgA production.[15] Although, at this time we do not advocate for use of alloSCT as a treatment option for uncomplicated autoimmune disease, the current case provides further evidence to support the curative potential of alloSCT for complex and debilitating immune diseases.

Concurrent IgA deficiency and platelet refractoriness due to anti HLA made the transfusion support of this patient particularly challenging. Plasma reduction and washed blood products in combination with premedication effectively reduced the occurrence of anaphylactic reactions from the IgA-containing products, thereby permitting a focus on HLA matching to secure hemostasis by the best possible platelet increments.

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doi:10.3324/haematol.2018.203943

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Koreth J, Schlenk R, Kopecky KJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: Systematic review and meta-analysis of prospective clinical trials. JAMA. 2009;301(22):2349–2361.
2. Fasslrinner F, Schetelig J, Burchert A, et al. Long-term efficacy of reduced-intensity versus myeloablative conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: retrospective follow-up of an open-label, randomised phase 3 trial. Lancet Haematol. 2018;5(4):e161–e169.
3. Lucarelli G, reviews G-J. Advances in the allogeneic transplantation for thalassemia. Blood Rev. 2008;22(2):53-63.
4. Filipovich A. Hematopoietic cell transplantation for correction of primary immunodeficiencies. Bone Marrow Transplant. 2008;42 Suppl 1:S49-S52.
5. Hough RE, Snowden JA, Wulffraat NM. Haemopoietic stem cell transplantation in autoimmune diseases: A European perspective. Br J Haematol. 2005;128(4):432–459.
6. Marusyk A, Polyak K. Tumor heterogeneity: Causes and consequences. Biochim Biophys Acta. 2010;1805(1):105–117.
7. Russel JA, Irish W, Balogh A, et al. The addition of 400 cGY total body irradiation to a regimen incorporating once-daily intravenous busulfan, fludarabine, and antithymocyte globulin reduces relapse without affecting nonrelapse mortality in acute myelogenous leukemia. Biol Blood Marrow Transplant. 2010;16(4):509–514.
8. Tobian AAR, Savage WJ, Tisch DJ, et al. Prevention of allergic transfusion reactions to platelets and red blood cells through plasma reduction. Transfusion. 2011;51(8):1676–1683.
9. Veeraputhiran M, Ware J, Dent J, et al. A comparison of washed and volume-reduced platelets with respect to platelet activation, aggregation, and plasma protein removal. Transfusion. 2011;51(5):1030–1036.
10. Hammarström L, Ringdén O, Lönnqvist B, Ringdén O, Smith CI, Wiebe T. Transfer of IgA deficiency to a bone-marrow-grafted patient with aplastic anaemia. Lancet. 1985;1(8432):778-781.
11. Rogers RL, Javed TA, Ross RE, et al. Transfusion management of an IgA deficient patient with anti-IgA and incidental correction of IgA deficiency after allogeneic bone marrow transplantation. Am J Hematol. 1998;57(4):326–330.
12. Hoekstra JH, Groot-Loonen JJ, van der Weij A, et al. Successful treatment of coeliac disease by allogeneic haematopoietic stem cell transplantation. J. Pediatr. Gastroenterol. Nutr. 2010;51(6):793–794.
13. Ciccocioppo R, Bernardo ME, Russo ML, et al. Allogeneic hematopoietic stem cell transplantation may restore gluten tolerance in patients with celiac disease. J Pediatr Gastroenterol Nutr. 2013;56(4):422–427.
14. Kline RM, Neudorf SM, Baron HI. Correction of celiac disease after allogeneic hematopoietic stem cell transplantation for acute myelogenous leukemia. Pediatrics. 2007;120(4):1120-1122.
15. Mielcarek M, Leisenring W, Torok-Storb B, Storb R. Graft-versus-host disease and donor-directed hemagglutinin titers after ABO-mismatched related and unrelated marrow allografts: evidence for a graft-versus-plasma cell effect. Blood. 2000;96(3):1150-1156.